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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,742	04/18/2001	Henry Daniell	CHL-T104XC1	6296

23557 7590 03/18/2005

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,742	DANIELL, HENRY	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/11/03, 1/27/04 5/27/04, 8/30/04, 1/3/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-18, 20, 21, 23-26 and 28-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19 and 22* is/are rejected.

7)☒ Claim(s) *27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group VIII (claims 19, 22 and 27) in the reply filed on 11 July 2003is acknowledged.

The traversal is on the ground(s) that Blowers et al only teaches vectors designed to confer herbicide resistance, a trait beneficial to the plant, while the instant invention confers no advantage to the plant and only produces proteins of value to humans. Applicant urges that they demonstrate assembly of multi-subunits and disulfide bond formation. This is not found persuasive. First, unity is lacking because the groups do not share a special technical feature; the process of recovering a biopolymer of Group X makes no use of the plastid transformation vectors of Groups I-IX and XI-XII. Second, not all of the plastid transformation vectors of groups I-IX and XI-XII encode proteins that have no benefit to the plant; the vector of group IV encodes the chaperonin of Cry2aA2 operon, which would assist in folding plastid proteins. Lastly, the claims are not drawn to vectors that encode multi-subunits, or to assembly of multi-subunits and disulfide bond formation.

Applicant urges that purification of the protein from the plants is required for the invention, and the use of biopolymers to precipitate proteins is part of the current invention. This is not found persuasive; claims 28 and 30 are merely drawn to a method of recovering a biopolymer by using a reversible property of the biopolymer; note that no method steps are recited. None of the groups I-XI and XII-XII are drawn to protein purification, and purification of the protein from plants transformed with those vectors could be accomplished by methods other than that of group X, and would be required for isolation of proteins other than biopolymers.

Applicant urges that the foreign proteins should be produce in large quantities, while Blowers et al only illustrate the production of small quantities of enzymes because they function catalytically, the herbicide resistance genes of Blowers did not require the codon optimization that the instant foreign genes did, several experimental strategies were developed for oral delivery of therapeutic proteins form plant cells. This is not found persuasive; the claims are not drawn to production of large quantities of proteins; codon optimization, or experimental strategies were developed for oral delivery of therapeutic proteins form plant cells.

The Declaration of Henry Daniell, filed 11 July 2003, states that he has read US Application 09/807,723; this is not found persuasive, as that is not the instant application.

The Declaration of Henry Daniell states that Ana Bailey, a co-inventor of the Blowers patent was a visiting professor in his laboratory and that an abstract to a meeting was submitted. However, in spite of repeated efforts expression of the glpA/B operon was unsuccessful and the abstract withdrawn.

This is not found persuasive because Bowers et al do teach that the operon was expressed in cells, callus and plants. Pg 56, line 14, to pg 57, line 8, teach that the construct successfully resulted in hph phosphotransferase activity and glyphosate resistance. Thus, Blowers et al do show that the operon was integrated and expressed. The patent of Blowers et al was not publically retracted for lack of enablement. Furthermore, the *glpA/B* operon is different than the *glpB-hph-aadA* construct of Blowers et al, and thus, lack of expression of the *glpA/B* operon does not provide evidence of lack of enablement of an operon comprising *glpB-hph-aadA*.

Applicant points to pg 6 and 51 of the instant specification, which states the invention is vectors capable of the production of high value pharmaceutical proteins by using fusion proteins

for hyperexpression and purification of the proteins, and that prior to Applicant's invention it was not known whether disulfide bonds existed in plant chloroplasts, and thus not known whether it was possible to express the pharmaceutical proteins in plants. This is not found persuasive. Not all the claimed vectors encode a fusion protein; *i.e.*, those of groups III, IV, VI-IX and XI. None of the claims are drawn to production of disulfide bonds in plants. Additionally, unity is lacking because the groups do not share a special technical feature; the process of recovering a biopolymer of Group X makes no use of plastid transformation vectors.

Applicant urges that Blowers et al does not teach or suggest creating a fusion protein that allowed hyperexpression and a one step purification process for pharmaceutical proteins. First, unity is lacking because the groups do not share a special technical feature; the process of recovering a biopolymer of Group X makes no use of the plastid transformation vectors of Groups I-IX and XI-XII. Second, not all the claimed vectors encode a fusion protein; *i.e.*, those of groups III, IV, VI-IX and XI.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-18, 20-21, 23-26 and 28-37 are withdrawn from consideration as being drawn to non-elected inventions.

2. The drawings filed 27 May 2004 are objected to because

The legends contain too many words; this information should be placed in the Brief Description of the drawings.

The Figure numbers for Figures 4-42 have a prior number crossed out and a new number inserted above; thus, these figures are informal.

Essential details cannot be made out in Figures 1B, 1C, 5-6, 10, 11, 12A, 12B, 13A-C, 14, 16, 17, 21, 24, 26A, 26B, 29A, 30A, 30B, 40 and, 41.

The tables should be a separate pages and not part of the drawings.

The following sets of figures appear to be identical to one another: Figures 4 and 15; Figures 5 and 16, Figures 6 and 17, Figures 7 and 18, Figures 8, 19 and 31; Figures 9 and 20; Figures 10 and 21; Figures 1 and 12, Figures 1CI and 13A; Figures 1CII and 13B; Figures 2A and 3B. All duplicate figures, including any not indicated, should be eliminated.

Portions of Figures 32, 34 and 36 are missing.

Corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. See 37 CFR 1.85(a) and MPEP 608.02(b).

3. The substitute specification amendment filed 18 April 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The substitute specification appears to contain substantial differences from the original specification. The examiner has done a cursory review of the specification, and support can not be found for the amendments. Although the each paragraph on pg 1-45 starts with a provisional application number, this does not indicate where in the positional application the paragraph, if it is quoted exactly, is found. No support at all is found for pg 46-107. Applicant is required to point to individual support for each sentence or paragraph, as appropriate, of the substitute specification or is required to cancel the new matter in the reply to this Office Action.

4. The substitute specification amendment filed 18 April 2004 is objected to because the paragraphs on pg 1-45 should not start with a provisional application number.

5. The abstract is not descriptive of the instant invention, which is a stable plastid transformation vector comprising a flanking sequence, a plastid promoter; a selectable marker sequence; a sequence encoding human serum albumin; a transcription termination region and a flanking sequence. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

6. The title of the invention is not descriptive of the instant invention, as above. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

Claim Objections

7. Claim 27 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

8. Claims 19 and 22 are objected to because of the following informalities:

In claim 19, line 2, "which" should be replaced with --, wherein the vector--.

In claim 19, line 5, the comma after "flanking" should be deleted.

Claim 22 starts with an improper article.

In claim 22, a comma is missing after "19".

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a stable plastid transformation vector comprising a flanking sequence, a plastid promoter; a selectable marker sequence; a sequence encoding human serum albumin; a transcription termination region and a flanking sequence.

The instant specification, however, only provides discussion of evaluation of chloroplast gene expression (example 1); protein expression (example 2); chemical and enzymatic cleavage of proteins (example 3); optimization of gene expression (example 4). The instant specification also provides prophetic guidance for plastid transformation vector construction (example 5); plastid transformation of tobacco (example 6); purification of protein from transformed plants (example 7); characterization and biological assays of the proteins (examples 8 and 9); animal testing and pre-clinical trials (example 10). The instant specification also provides guidance for transformation of tobacco plastids with a vector encoding the cholera toxin B subunit (pg 77-83).

The instant specification fails to provide guidance for a stable plastid transformation vector comprising a flanking sequence, a plastid promoter; a selectable marker sequence; a

sequence encoding human serum albumin; a transcription termination region and a flanking sequence.

The region of the tobacco plastid genome commonly used for targeting of transformation vectors is not present in the same configuration in the plastid genomes of other economically important plants; for example, rice (Kanno et al, 1993, Curr. Genet. 23:166-174) lacks the orf131/orf70B gene (see Figure 3).

The specification fails to teach a region of the plastid genome that is homologous across all plant species.

The instant specification also fails to teach transformation of the plastids of any plant species other than tobacco. Heifetz (2000, Biochimie 82:655-666) teaches that reliable and efficient plastid transformation and regeneration of fertile plants with transformed plastids has been limited to tobacco and potato (pg 658, right column, paragraph 2). Heifetz also indicates that stable plastid transformation requires regeneration of fertile plants with transformed plastids (pg 656, left column, paragraph 1) and that segregation to the homoplastic state is the factor limiting plastid transformation to solanaceous plants (pg 658, right column, paragraph 2).

As the specification does not describe the transformation of any plant with a plastid transformation vector comprising a flanking sequence, a plastid promoter; a selectable marker sequence; a sequence encoding human serum albumin; a transcription termination region and a flanking sequence, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those that express human serum albumin, if such plants are even obtainable.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate the claimed plastid transformation vectors.

11. Claims 19 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a stable plastid transformation vector comprising a flanking sequence, a plastid promoter; a selectable marker sequence; a sequence encoding human serum albumin; a transcription termination region and a flanking sequence. In contrast, the specification only describes a plastid transformation vector that encoding the cholera toxin B subunit. Applicant does not describe any vectors encompassed by the claims, and the structural and functional features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described stable plastid transformation vector comprising a flanking sequence, a plastid promoter; a selectable marker sequence; a sequence encoding human serum albumin; a transcription termination region and a flanking sequence, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 19 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claim 19 lacks antecedent basis for the limitations "said plastid" in line 3, "the target plastid genome" in line 7, "the heterologous coding sequence" in lines 7-8, "the target plant" in line 8, "the flanking sequence" in line 9, "the homologous sequences" in line 9, and "the target plastid genome" in lines 9-10.

Claim 19 is indefinite in its recitation of "DNA sequence coding for a ...gene" in lines 4-5. It is unclear how a DNA sequence can code for a gene; a DNA sequence can only encode a protein or a RNA. Additionally, genes comprise promoters.

Claim 19 is indefinite in its recitation of "throughout homologous recombination" in lines 8-9. This phrase makes no sense. Should "throughout" be replaced with --through--?

Claim 22 is indefinite in its recitation of "HSA is fused to a 5'UTR sequence positioned upstream of the promoter". HSA is a protein encoded by the vector of claim 19; 5'UTRs are nucleic acids. Is applicant claiming a nucleic acid fused to a protein? Does Applicant mean that the sequence encoding HSA is fused to a 5'UTR? If the latter, 5'UTrs are located downstream of the promoter, not upstream.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daniell (WO 99/10513 A1).

The claims are drawn to a plastid transformation and expression vector comprising an expression cassette comprising a plastid promoter, a selectable marker sequence, a heterologous DNA encoding human serum albumin, and a plastid transcription termination region, wherein the vector also comprises flanking sequences homologous to plastid DNA.

Daniell teaches a plastid transformation and expression vector comprising an expression cassette comprising a plastid promoter (the *Prrn* promoter), a selectable marker sequence (the *aadA* gene), a heterologous DNA encoding proinsulin, and a plastid transcription termination region (*psbA* 3'), wherein the vector also comprises flanking sequences homologous to plastid DNA (the *rbcl* and *orf512* genes) and methods of using the vector in plastid transformation (pg 29, line 19, to pg 33, line 19; pg 51, line 12, to pg 60, line 9; Fig 3A; claims 1-2, 85-86, 100-103 and 111-113). Daniell do not disclose plastid transformation vectors encoding human serum albumin.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the plastid transformation vectors taught by Daniell, to encode human serum albumin. One of ordinary skill in the art would have been motivated to do so because of the

suggestion of Daniell to do so (pg 14, line 17-18, pg 32, line 1, pg 33, lines 10-19, and claim 105).

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Anne R. Kubelik, Ph.D.
March 7, 2005